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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
10/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,488	TJOTTA, ENOK	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,30-34,37,38 and 40-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,30-34,37,38 and 40-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/07/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed July 22, 2010 in response to the Office Action of April 22, 2010 is acknowledged and has been entered. Previously pending claims 1-27, 29, 35, 36, 39, have been cancelled, claims 28, 40, 45, 48, 51, , 52, 54, 60, 61 have been amended and new claims 62 and 63 have been added. Claims 28, 30-34, 37, 38, 40-62 and 63 are currently being examined.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 51-53, 55, 60 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in section 9 of the Office Action of April 22, 2010, which are set forth below.

. . . because the specification, while being enabling for a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, and acetyl salicylic acid, *does not* reasonably provide enablement for a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, analogues thereof, and analogues of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, and acetyl salicylic acid, or wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 60 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, Mito+, or

Benzo(a)pyrene, *does not* reasonably provide enablement for a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof or analogues of insulin, insulin like growth factors, conditioned medium, serum factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor , wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4- [2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof. The claims encompass inhibiting clonal cell growth in any cell type *in vitro* or *in vivo* with the claimed compounds and unlimited analogues thereof.

Claim 60 is broadly drawn to a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof. The claim encompass stimulating clonal cell growth in any cell type *in vitro* or *in vivo* with the claimed compounds and unlimited analogues thereof

It is noted that although claims 48, 51, and 60 depend from independent claims that use the method of claims 28 to identify clonal mitotic inhibitors or stimulators, the inhibitors of claims 48, 51, and 60 were not identified by the method of claim 28 and do not necessarily have the properties of a clonal inhibitor or stimulator.

The specification teaches that 4-OH-OPB could inhibit the development of Ehrlich ascites tumors when injected with the tumor cells. See Experiment 8 and 9. The specification teaches that 4-OH-OPB could inhibit the development of spleen antibody producing cells. See Experiment 10.

The specification teaches that 4-OH-OPB could inhibit the HSV viral production in culture. See Experiments 11 and 12.

The specification teaches that 4-OH-OPB inhibited the clonal growth of S100T1 cells in low density cell soft agar culture in and did not inhibit clonal cell growth in high density cultures. See Experiment 13- 25.

The specification teaches that colchicine inhibited the clonal growth of S100T1 cells in low density cell soft agar culture in and did not inhibit clonal cell growth in high density cultures. See Experiment 13, 15-18.

The specification teaches that diclofenac did not inhibit the clonal growth of S100T1 cells soft agar culture and may have shown slight stimulatory effect. See Experiment 15.

The specification teaches that ibuprofen, naproxen, and acetyl salicylic acid, inhibited the clonal growth of S100T1 cells soft agar culture. See Experiments 15 and16.

The specification teaches that 2-Butyl-N-(4-hydroxy-phenyl)-N'-phenylmalonamide did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22, 23, and 25.

The specification teaches that 1, 2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22 and 25.

The specification teaches that p-hydroxy-azobenzene did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 23 and 25.

The specification teaches that Benzo (a) pyrene weakly stimulated the clonal growth of S100T1 cells in low density cell soft agar culture. See Experiment 26.

The specification teaches that Sulindac had stimulatory and inhibitory effects on the clonal growth of S100T1 cells l soft agar culture. See experiment 26.

The specification teaches that the serum extender Mito+, insulin and conditioned medium stimulated growth in of BHK21/C13 cells in soft agar. See Experiment 3 and page 57.

One of skill in the art cannot extrapolate the teachings of the specification to enable the full scope of the claims to use all of the compounds claimed in claims 48, 51 and 60 clonal mitotic inhibitors and stimulators in any cell type under any condition because some of the claimed compounds have been only tested for their activity *in vitro* against one cultured cell type (S100T1). These effects cannot be predictably extrapolated to clonal inhibition or stimulation to any cell type under any condition because cultured cells can produce artifactual responses that are not reflective of the *in vivo* response of cells and cells are heterogeneous in the phenotypes and responses to drugs like clonal mitotic inhibitors or stimulators.

In particular as drawn to cell culture artifacts, the characteristics of cultured cell lines generally differ significantly from the characteristics of cells in a whole organism. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an

evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-cell and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al. (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109. Thus, the unpredictability of extrapolating *in vitro* cell data to the *in vivo* situation is well known in the art.

In addition, clonal mitotic inhibitors or stimulators must accomplish several tasks to be effective *in vivo*. They must be delivered into the circulation that supplies the cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition variables such as biological stability, half-life or clearance from the blood are

important parameters in achieving successful delivery of these agents. The clonal mitotic inhibitors or stimulators may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life. In addition, the clonal mitotic inhibitors or stimulators may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the clonal mitotic inhibitors or stimulators and a large enough local concentration may not be established.

Thus, based on the effects in the specification observed with a single cell line in vitro, one of skill in the art would not predictably expect that all of the claimed compounds or analogues thereof would inhibit or stimulate clonal growth in any cell type under any condition *in vivo* or *in vitro*. Thus, undue experimentation would be required to make and use the method as broadly claimed.

Additionally, as drawn to the heterogeneity of cell phenotypes, Busken, C. et al. (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore, Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. (Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C). Additionally, USPN 6,258,845 (Gerner et al. July 10, 2001) teaches that sulindac inhibits colon carcinogenesis in a rat model by the induction of apoptosis. See Col. 1-lines 34-45. Thus, one of skill in the art would not expect that sulindac to be a clonal mitotic stimulator in all cell types treated with it. Furthermore, USPN 4,880, 742 (Hayaishi et al. 1989) teach that Diclofenac inhibits the growth of T-cells with the AIDS virus. See Fig. 1 and 2 and claim 1. Thus, one of skill in the art would not expect that Diclofenac to be a clonal mitotic stimulator in all cell types treated with it. Given the above, one of skill in the art would not predictably be able inhibit or stimulate clonal growth in any cell type under any condition with the all of claimed compounds and analogs thereof without undue experimentation.

Additionally as drawn to claim 55 wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells, one of skill in the art would not predictably expect to remove the collocated infected cells because HIV and the herpes simplex viruses form latent infections in cells that are not removed from the subject by treatments for these diseases used at the time the invention was made. In particular, Dybul et al. (MMWR Recommendations and Reports May 17, 2002, p.1-71) teach that eradication of HIV

infection cannot be achieved with available anti-retroviral regimens, because the pool of latently infected CD4+ T cells is established early during infection and persists with a long half-life. See p. 13. Additionally, Efstathiou and Preston (Virus Res. 2005, 111:108-119) teach that a key characteristic of all herpes viruses is their ability to establish life-long latency within the infected host. See p. 108. Additionally, Smith et al. (Antiviral Res. 2001 52:19-24) teach that herpes simplex virus drugs like acyclovir have no effect on the latent HSV infection once established. See ¶ bridging p. 20 and 21 and p. 23. Thus, given the resistance of latent HIV and HSV infections to anti-viral treatments known at the time the invention was made, one of skill in the art would not be able to remove the collocated infected cells with methods known in the art or taught in the specification without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

Applicant argues that regarding enablement (item 9) the Office Action comments at page 20, third paragraph:

> One of skill in the art cannot extrapolate the teachings of the specification to enable the full scope of the claims to use all of the compounds claimed in claims 48, 51 and 60 clonal mitotic inhibitors and stimulators in any cell type under any condition because some of the claimed compounds have been only tested for their activity in vitro against one cultured cell type (S1OOT1). These effects cannot be predictably extrapolated to clonal inhibition or stimulation to any cell type under any condition because cultured cells can produce artifactual responses that are not reflective of the in vivo response of cells and cells are heterogeneous in the phenotypes and responses to drugs like clonal mitotic inhibitors or stimulators.

Applicant argues that in response, the applicant notes that it is correct that the screening part of the claimed test is not enough for accepting the compounds as adequate treatment for stopping metastases. Therefore, a test in living organisms is essential and is included in the patent claim (see Experiments 7-9). At the moment none of the tested compounds have shown as good results as 4-OH-OPB in vitro and in vivo.

Applicant argues that however, less activity in this respect may also be interesting and it can explain why persons using for instance acetylsalicylic acid (see experiment 15 and 16) is known to be partly protected against development of cancer. On the other hand, detected activities as stimulators of clonal growth (see Experiment 26) may be important when testing food or other compounds in our environment, since this activity is expected to have the opposite effect; increasing the incidence of cancer or stimulating the progression of this disease.

Applicant argues that the in vitro test on cell lines is not as bad as given voice to in the Official Action, since the best clonal inhibitor, 4-OH-OPB, shows no breakthrough in the agar cultures of clones with ability to grow even when under treatment. The best example of the opposite is Colchicine that is not stopping all clones, but let a few grow even at high concentrations of Colchicine. In our experiments this compound is rather not able to save mice transplanted with Ehrlich's cancer cells (see Experiment 18).

Applicant argues that in addition the Office Action states in the first paragraph of page 23 that: *'Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived.*"

Applicant argues that cancer cells with or without changes is not the question. All cells that the inventor has tested, even normal cells in culture or in the organism (see Experiment 10) react the same way on specific clonal inhibition. Single or very few immune-cells in the spleen among other non-identical immune-cells are inhibited. Collocated identical cells in other organs in the animal (liver, muscles, skin, peritoneum etc) are not inhibited by specific clonal inhibitor and can not abrogate the effect of a specific clonal inhibitor on scattered identical cells in close

contact (see Experiments 7-9). This stresses the importance of the main invention, a basic biological and medical principle with many practical consequences.

Applicant's arguments have been considered, but have not been found persuasive. As drawn to inhibiting clonal growth in a subject, although 4-OH-OPB and acetyl salicylic acid have been shown to inhibit cell growth and were found to be enabled, several of the other claimed agents for inhibiting cell growth have been shown to have little effect. As previously set forth, the specification teaches that 2-Butyl-N-(4-hydroxy-phenyl)-N'-phenylmalonamide did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22, 23, and 25. The specification teaches that 1, 2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5- pyrazolidinedione did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22 and 25. The specification teaches that p-hydroxy-azobenzene did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 23 and 25. Additionally, the specification provides no evidence on the ability of the broadly claimed analogues of the compounds of claim 51 to inhibit clonal cell growth in a subject or serum extenders to stimulate clonal cell growth. Although collocated cells may share some properties, as previously set forth, it is well understood in the art that cells of distinct tissues and diseases behave differently and respond differently to drugs and, as Applicant apparently agrees, the in vitro cell culture testing is not predictably indicative of in vivo results. Thus, in absence of sufficient evidence that p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, analogues thereof, and analogues of

4-OH-OPB, colchicine, Ibuprofen, Naproxen, and acetyl salicylic acid will inhibit clonal cell growth in a subject or that serum extenders will stimulate cell growth, the rejections is maintained for the reasons previously set forth and above.

Applicant argues that on the second paragraph of page 25 the Office action asserts:

> Additionally as drawn to claim 55 wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells, one of skill in the art would not predictably expect to remove the collocated infected cells because HIV and the herpes simplex viruses form latent infections in cells that are not removed from the subject by treatments for these diseases used at the time the invention was made. In particular, Dybul et al. (MMWR Recommendations and Reports May 17, 2002, p.1-71) teach that eradication of HIV infection cannot be achieved with available anti-retroviral regimens, because the pool of latently infected CD4+ T cells is established early during infection and persists with a long half-life. See p. 13. Additionally, Efstathiou and Preston (Virus Res. 2005, 111:108-119) teach that a key characteristic of all herpes viruses is their ability to establish life-long latency within the infected host. See p. 108. Additionally, Smith et al. (Antiviral Res. 200152:19-24) teach that herpes simplex virus drugs like acyclovir have no effect on the latent HSV infection once established. See ¶ bridging p. 20 and 21 and p. 23. Thus, given the resistance of latent HIV and HSV infections to anti-viral treatments known at the time the invention was made, one of skill in the art would not be able to remove the collocated infected cells with methods known in the art or taught in the specification without undue experimentation.

Applicant argues that in response, applicant respectfully notes that it is correct that it is not considered possible to remove all infected cells from HIV infected patients. However, it might be possible to remove a large portion of them, e.g., by using antibodies with toxic groups to cells expressing HIV antigens or by simply using cytotoxins. The latter method is used in connection with bone marrow transplantation, but might be risky.

Applicant argues that at the moment there is no final proof, but many indications that removing many of these cells with inactive HIV would dilute their local crowding and allow better inhibitory effect of 4-OH-OPB on the production of active HIV. This viewpoint is a central part of the invention and is not known in previous art, e.g., in TJOTTA.

Applicant argues that for Herpes a method similar to the first one for HIV might also be possible, and may be easier since the crowding of chronically infected cells in nerve ganglia probably is less than the crowding of cells containing HIV genome in the lymphatic organs.

Applicant's arguments have been considered, but have not been found persuasive because the claim is not limited to removing a large portion of the HIV infected cells, rather it is drawn to removing collocated infected cells, which encompasses removing all of the collocated infected cells. Furthermore, no evidenced has been provided that the treatments suggested by Applicant are effective. Given the difficulty in treating the infected cells taught in the art and in absence of the evidence to the contrary, undue experimentation would be required to use the method as claimed.

3. Claims 51-53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in section 10 of the Office Action of April 22, 2010, which are set forth below.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor , wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4- [2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof.

Claim 60 is broadly drawn to a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof.

The specification does not put any limit on the analogues of the claimed compounds. Thus, the instant method claims are reliant on the identity of a large genus of analogues to inhibit or stimulate clonal cell growth. When given the broadest reasonable interpretation, the term

"analogues" encompasses any type of compound with little or not structural similarity to the claimed compounds, which can inhibit or stimulate clonal cell growth. The description of the various claimed compounds fails to adequately describe the genus of analogues because said genus tolerates members which differ significantly in both structure and function from that of the claimed compounds. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of "analogues" of the claimed compounds at the time the invention was filed. Because the genus of "analogues" is not adequately described, the method claims relying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of analogues of the claimed compounds, per Lilly by structurally describing a representative number of analogues of the claimed compound, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe analogues of the claimed compounds, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide any functional characteristics coupled with a known or disclosed correlation between structure and function for analogues of the claimed compounds. Although the specification discloses the claimed compounds, this does not provide an adequate description of analogues of the claimed compounds that would satisfy the standard set out in Enzo.

The specification also fails to describe analogues of the claimed compounds by the test set out in Lilly. The specification describes only the claimed compounds a few related compounds. Therefore, it necessarily fails to describe a "representative number" of species of analogues of the claimed compounds. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of analogues of the claimed compounds that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

Applicant argues that at the third paragraph of page 26 the Office Action asserts:

Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p~hydroxy-azobenzene, 2-Butyl-2- hydroxy-N- (4- hydroxy-phenyl) -N'-phenyl malonamide, 1, 2-diphenyl-4-hydroxy-4- [2- (phenylsulfinyl) ethyl] - 3,5-pyrazolidinedione, and analogues thereof.

Applicant argues that however, analogues of 4-OH-OPB are described in the patent application on pages 45-47 of PCT/N02003/000335:

Some 4-hydroxy-3,5-dioxo-pyrazolidines are described in the literature for treatment of HIV infections and some other viral infections, tropic spastic paraparesis, autoimmune diseases, transplantation rejection and special tumours as Sezary syndrome, mycosis fungoides, T-cell lymphoma, and Kaposis sarcoma. The example used in the described experiments is 4-OH-OPB, which is 4-butyl-4-hydroxy-2 (p-hydroxyphenyl) -1 -phenyl-3, 5-pyrazolidinedione with the general formula:

Rc Rd
\ /
N__N
0=/ \=0
\ /
/ \
R_bO R_a

where Ra - Rd might be defined as in Table1.

The immunosuppressive and antineoplastic drugs available might have inhibiting effects on clonability of tumour cells, and possibly also inhibit metastatic migration.

However, collocated cells might partly or fully neutralise the effect on clonability if the substances have low toxicity. This knowledge is probably very important when treating patients, especially those with malignant diseases. Since most of the cytotoxic drugs used against cancer also are expected to have a smaller or greater effect against clonal growth, there are possibilities of finding suitable candidates among them that could be used in reduced, less toxic concentrations over long time periods giving effects as described for clonal inhibitors.

Therefore, the substances exemplified in the following might be potential candidates and is currently tested by the method of the invention in the inventor's laboratory.

Table 1 is reproduced.

Applicant argues that it is thus believed that the instant claims of the present invention comply with the written description requirement and are sufficiently enabled such that one of skill in the art can practice the claimed invention without recourse to undue experimentation.

Applicant's arguments have been considered, but have not been found persuasive because the analogues of the claims are not limited to analogues of 4-OH-OPB. Furthermore, although 4-OH-OPB inhibits clonal cell growth and the specification recites potential analogues of 4-OH-OPB, the specification has not established a correlation between the structure and function of the broadly claimed analogues of 4-OH-OPB or analogues any of the claimed compounds and inhibiting clonal cell growth. Thus, the specification does not provide an adequate written description of the analogues of the compounds of claims 51-53 for the reasons previously set forth and above.

4. Claims 54-56 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth in section 11 of the Office Action of April 22, 2010, which are set forth below

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations of "wherein 4-OH-OPB is administered to a subject after said subject has been exposed or infected to HIV and before HIV infected cells are piling up", "wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells", and "wherein 4-OH-OPB is administered in combination with an anti-viral treatment to inhibit drug resistance" claimed in Claims 54-56 have no clear support in the specification and the claims as originally filed. Applicants pointed Examples 10-12 in the Remarks of 01/11/2008 for support of claims 54-56. A review of the specification discloses support for testing the effect of 4-OH-OPB on the number of cells in spleen with production of antibodies against sheep red cells after immunization (Experiment 10); testing herpes virus type

1 for sensitivity to 4-OH-OPB (Experiment 11); and testing herpes virus type 2 for sensitivity to 4-OH-OPB (Experiment 12). The suggested support is not found persuasive because there is nothing in the specification to suggest the specific treatments claimed in claims 54-56. The subject matter claimed in claims 54-56 broadens the scope of the invention as originally disclosed in the specification.

Applicant did not specifically present arguments with regard to this rejection and the amendment to claim 54 does not obviate this rejection. As the arguments presented do not apply to this rejection, the rejection is maintained for the reasons previously set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 47-54, 56, 57, 59 and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/00585 (Tjotta et al. 4 January 2001, IDS) evidenced by Szucs et al. (Bulletin World Health Org. 1988 66: 729-737) for the reasons set forth in section 12 of the Office Action of April 22, 2010, which are set forth below.

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

WO 01/00585 (Tjotta et al. 4 January 2001) teach inhibition of T-lymphocyte growth, T-cell tumor growth and Kaposi's sarcoma with pyrazolidinols, including 4-OH-OPB. WO 01/00585 teaches treating subjects with HIV and Herpes infection with 4-OH-OPB, Which would be before HIV infected cells are piling up given the undefined time before HIV infected cells are piling up. See Abstract, pages 1-10, and claims 1-12. WO 01/00585 teaches administering additional antiviral agents with 4-OH-OPB to inhibit drug resistance. See claim 5 and ¶ bridging p. 5and 6. WO 01/00585 teaches adding fresh growth media to MT-4 cells, Additionally, Szucs et al. teach that MT-4 are grown in serum. See p. 730-1st col. Thus, one of

skill in the art would immediately recognize that MT-4 cells are grown in serum. See Example 12. Although, WO 01/00585 does not specifically teach that T-lymphocyte growth and Kaposi's sarcoma is clonal cell growth, in the absence of a limiting definition of clonal cell growth, WO 01/00585 anticipates the claims.

Although the reference does not specifically state that 4-OH-OPB was administered as an initial treatment in order to inhibit metastasis of a cancer, the claimed method appears to be the same as the prior art product, absent a showing of unobvious differences as the administered 4-OH-OPB would inherently have this property . The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants argue that in regards to the new rejection over TJOTTA et al. as evidenced by SZUCS et al. set forth on page 31, the Office Action states:

> [I]t is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.
>
> WO 01/00585 (Tjotta et al. 4 January 2001) teach inhibition of T-lymphocyte growth, T-cell tumor growth and Kaposi's sarcoma with pyrazolidinols, including 4-OH-OPB. WO 01/00585 teaches treating subjects with HIV and Herpes infection with 4-OH-OPB, Which would be before HIV infected cells are piling up given the undefined time before HIV infected cells are piling up. See Abstract, pages 1-10, and claims 1-12. WO 01/00585 teaches administering additional antiviral agents with 4-OH-OPB to inhibit drug resistance. See claim 5 and ¶ bridging p. 5 and 6. WO 01/00585 teaches administering additional antiviral agents with 4-OH-OPB to inhibit drug resistance. See claim 5 and ¶ bridging p. 5 and 6. WO 01/00585 teaches adding fresh growth media to MT-4 cells, Additionally, Szucs et al. teach that MT-4 are grown in serum. See p. 730-1st col. Thus, one of skill in the art would immediately recognize that MT-4 cells are grown in serum. See Example 12. Although, WO 01/00585 does not specifically teach that T-lymphocyte growth and Kaposi's sarcoma is clonal cell growth, in the absence of a limiting definition of clonal cell growth, WO 01/00585 anticipates the claims. Although the reference does not specifically state that 4-OH-OPB was administered as an initial treatment in order to inhibit metastasis of a cancer, the claimed method appears to be the same as the prior art product, absent a showing of unobvious differences as the administered 4-OH-OPB would inherently have this property . The office does not have the facilities and resources to provide the factual evidence needed in order to establish

that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

This argument by the Office is based on two paragraphs [0028] and [0031] in TJOTTA et al.:

[0028] However, in a particularly preferred embodiment of the invention, a pyrazolidinol according to the invention is administered at a dose sufficient to suppress T-lymphocyte (CD4 and CD8 cell) growth (e.g. a daily dose of 0.i to i0 ~mol/kg) for a period of 1 to 14 days, preferably 2 to 7 days at intervals of at least 3 months, preferably at least 9 months, e.g. i0 to 18 months. In this way the patient's immune system may be "refreshed" by removal of the preponderance of T-lymphocytes directed to HIV antigens. Such a treatment indeed is novel and forms a further aspect of the invention. Viewed from this aspect the invention provides a method of combating HIV infection which comprises administering to an HIV- infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system, e.g. the lymph nodes, in said patient by at least 25%, more preferably at least 50%, said administration being repeated at intervals of at least 3 months, preferably at least 9 months.

[0031]Besides HIV, the pyrazolidinols of the invention may be used to combat other viral infections, especially retroviral infections but also infections by togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calci viridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, herpes virus and arenaviridea. The pyrazolidinols of the invention may in particular be used to combat viral infection of CD4 cells, e.g. HIV-I, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary

> Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma. Moreover despite not being of the accepted formula for NSAIDs (which would require an acid proton in place of RIXI at the 4-position), they may be used as anti- inflammatory drugs. All these uses form aspects of the invention.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts:

> Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of TJOTTA

anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators of the prior art for the reasons previously set forth. Claim 61 is not connected to the rejected claims. Thus the rejection is maintained.

Applicant argues that t is evident from patent TJOTTA (paragraph 31, 7 lines from end) that: "The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-I, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma."

Applicant argues that this paragraph teaches that the pyrazolidinols should combat: T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours).

Applicant argues that this is 5 tumors. This shows that at the time TJOTTA was filed nobody knew that growth of tumors are not affected by 4-OH-OPB. Therefore, it is evident that the knowledge where tumors neutralized the effect of what we now call specific clonal inhibitors was not a part of prior art at that time. Even the growth of T4-cell tumors will not be affected by specific clonal inhibitors since the claimed patent applies the T4 cell line MT4 that reacted just as other cells in culture. The inhibitory growth effect of the best known specimen of these compounds, 4-O-OPB, was much more pronounced on sparsely seeded cells than on cultures containing many cells (see experiment no. 14).

Applicant argues that the present invention is thus clearly distinguished from the prior art such that there is neither anticipation nor prima facie unpatentability. These rejections are believed to be overcome and withdrawal thereof is respectfully requested.

Applicant's arguments have been considered, but have not been found persuasive. Whether or not at the time TJOTTA was filed nobody knew that growth of tumors are not affected by 4-OH-OPB, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. See MPEP 2112. Given that 4-OH-OPB is claimed as clonal mitotic inhibitor and the specification shows that it has this function, TJOTTA anticipates the claimed methods. Furthermore, similarly the serum factors in the serum in the fresh growth media added to the MT4 cells in TJOTTA, see Example 12, would inherently be clonal mitotic stimulators as claimed with the ability to stimulate clonal cell growth. Thus, the rejection is maintained for the reasons previously set forth.

6. Claims 47-53, 59 and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by USPN 6,258,845 (Gerner et al. July 10, 2001) for the reasons set forth in section 13 of the Office Action of April 22, 2010, which are set forth below.

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

USPN 6,258,845 treating cells and subjects with acetyl salicylic acid (aspirin), ibuprofen, and sulindac for the treatment of cancer. See claims, col. 1, col. 5-lines 40-66, col. 8-line 50 to col. 10-line 20, Figs. 1-8, Examples 1-6. USPN 6,258,845 teaches culturing caco-2 in fetal bovine serum and sulindac and performing clonogenic assays. See Example 1 and Fig. 1-4. It is noted that all individuals have at least some level of risk for the conditions of claim 52 and 53, thus these individuals would be treated by the methods of USPN 6,258,845. Given that acetyl

salicylic acid (aspirin), ibuprofen, and sulindac are used for the treatment of cancer they would be administer at amounts effective to inhibit clonal cell growth.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts :

> Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of Gerner et al. anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the

products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators of the prior art for the reasons previously set forth. Claim 61 is not connected the rejected claims. Thus the rejection is maintained.

7. Claims 47-53, 59 and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by USPN 4,880,742 (Hayaishi et al. 1989) evidenced by McClain et al. (FASEB Journal, 1995 9: 1345-1354) for the reasons set forth in section 14 of the Office Action of April 22, 2010, which are set forth below.

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

USPN 4,880,742 teaches treating Molt-4 leukemia cells with Diclofenac, which is encompassed by "analogues" in claims 48 and 51 in amounts effective to kill the cells, which would inhibit their clonal cell growth. See Example 6, Fig. 1 and 2, and claim 1. USPN 4,880,742 also teaches treating with effective amounts of aspirin (acetyl salicylic acid), naproxen, sulindac, and ibuprofen for therapy. See Col. 1-4.

McClain et al. (FASEB Journal, 1995 9: 1345-1354) teach that MolT-4 cells are grown in fetal bovine serum. See p. 1346-1st col. Thus, one of skill in the art would have inherently recognized that the Molt-4 cells of USPN 4,880,742 are grown in serum to stimulate clonal cell growth.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts :

> Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for

the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of Hayaishi et al. anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators of the prior art for the reasons previously set forth. Claim 61 is not connected the rejected claims. Thus the rejection is maintained.

8. Claims 47, 48, 59 and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by De Asua et al. (Proc. Natl. Acad. Sci. USA, 1973, 70: 1388-13920, previously cited) for the reasons set forth in section 15 of the Office Action of April 22, 2010, which are set forth below.

It is noted that the clonal mitotic inhibitor of claims 47 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it

which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in 47 and 59 need not be selected by the method of claim 28.

De Asua et al. teach stimulating the clonal growth of BHK21/13 cells with serum and insulin and inhibiting clonal growth with cAMP, which would be encompassed by the broadly claimed analogue. See p. 1388- 2nd col., p. 1389. Fig. 1-5.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts :

> Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of De Asua et al. anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators for the reasons previously set forth. Claim 61 is not connected the rejected claims Thus the rejection is maintained.

9. Claims 47, 48, 59 and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kamei H. (Cell Biol. Int. Rep. Jan. 1987, 11 (1): 35-41, previously cited)) for the reasons set forth in section 16 of the Office Action of April 22, 2010, which are set forth below.

It is noted that the clonal mitotic inhibitor of claims 47 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in 47 and 59 need not be selected by the method of claim 28.

Kamei teaches stimulating the clonal growth of BHK21/13 cells with serum and insulin and inhibiting clonal growth with retinoic acid, which would be encompassed by the broadly claimed analogue. See p. 35, 36., Table 1 and 2, Fig. 1 and 2.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts:

> Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have

been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of Kamei anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators of the prior art for the reasons previously set forth. Claim 61 is not connected the rejected claims. Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claim 58 remains rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/00585 (Tjotta et al. 4 January 2001, IDS) in view of Tannock, I.F. (*Experimental Chemotherapy*, Ch. 19-p. 338 and 352-359, in The Basic Science Of Oncology Tannock and Hill, eds., New York 1992) for the reasons set forth in section 17 of the Office Action of April 22, 2010, which are set forth below.

WO 01/00585 teaches as set forth above, but does not teach administering 4-OH-OPB to a subject undergoing conventional cancer treatment.

Tannock teaches that it has become common practice to treat cancer patients with multiple anti-cancer agents to enhance the tumor response over that of the individual agents. See p. 352-2nd col.., p. 353-1st col., p. 357- 2nd col. and Table 19.3. Tannock teaches that improvements in clinical chemotherapy have depended largely on the use of drugs in combination. See p. 338.

It would have been *prima facie* at the time the invention was made to combine the treatment of T-cell tumors and Kaposi's sarcoma with 4-OH-OPB with conventional cancer treatment because Tannock teaches that it is common practice to treat cancer patients with multiple anti-cancer agents to get an enhanced anti-tumor response. One of skill in the art would have been motivated to find the optimal treatment for cancers like T-cell tumors and Kaposi's sarcoma by combining the 4-OH-OPB treatment with conventional chemotherapy. Given that that the claimed compounds were known in the art for cancer treatment, one of skill in the art would have had a reasonable expectation of success of using the compounds in combination.

Applicant argues that distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

At page 13, third full paragraph the Office Action asserts:

Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's [arguments] are not found persuasive and the rejection is maintained.

Applicant argues that however, independent claims 28 and 61 have been amended to add subject matter that the Office infers may be allowable. This includes specifying the agent as "an agent that has an activity on clonal growth," seeding "solitary" cells on "soft" agar and a "low gelling temperature gel". Support for these amendments can be found at pages 27 and 40 of the specification.

Applicant argues that the claimed invention is thus clearly allowable over the previously applied art.

Applicant's arguments have been considered, but have not been found persuasive. Although claim 28 has been amended, the clonal mitotic inhibitors and stimulators of TJOTTA anticipate the clonal mitotic inhibitors and stimulators claimed because regardless of how the products are obtained or identified they are the same as the clonal mitotic inhibitors and stimulators of the prior art for the reasons previously set forth. Claim 61 is not connected the rejected claims. Thus the rejection is maintained.

Applicant argues that t is evident from patent TJOTTA (paragraph 31, 7 lines from end) that: "The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-I, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat

AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma."

Applicant argues that this paragraph teaches that the pyrazolidinols should combat: T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours).

Applicant argues that this is 5 tumors. This shows that at the time TJOTTA was filed nobody knew that growth of tumors are not affected by 4-OH-OPB. Therefore, it is evident that the knowledge where tumors neutralized the effect of what we now call specific clonal inhibitors was not a part of prior art at that time. Even the growth of T4-cell tumors will not be affected by specific clonal inhibitors since the claimed patent applies the T4 cell line MT4 that reacted just as other cells in culture. The inhibitory growth effect of the best known specimen of these compounds, 4-O-OPB, was much more pronounced on sparsely seeded cells than on cultures containing many cells (see experiment no. 14).

The present invention is thus clearly distinguished from the prior art such that there is neither anticipation nor prima facie unpatentability. These rejections are believed to be overcome and withdrawal thereof is respectfully requested.

Applicant's arguments have been considered, but have not been found persuasive. First one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Additionally, whether or not at the time TJOTTA was filed nobody knew that growth of tumors are not affected by 4-OH-OPB, there is no requirement that a person of ordinary skill in the art would

have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. See MPEP 2112. Thus, TJOTTA and Tannock make obvious the claimed methods for the reasons previously set forth. Furthermore, similarly the serum factors in the serum in the fresh growth media added to the MT4 cells in TJOTTA, see Example 12, would inherently be clonal mitotic stimulators as claimed with the ability to stimulate clonal cell growth. Thus, the rejection is maintained for the reasons previously set forth

New Grounds of Rejection

Claim Objections

11. Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The clonal test of claim 28 is now being performed in soft agar medium and a low gelling temperature gel. Claim 30 recites the clonal test is performed in: i) a fluid medium, or ii) a semisolid or solid medium, which is broader than the medium of claim 28, i.e. soft-agar or low gelling temperature gel.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 60 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60 contains the trademark/trade name Mito+. See BD Biosciences (Mito+ Serum Extender, 2010). Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a clonal mitotic stimulator and, accordingly, the identification/description is indefinite.

Additionally, the terms "potential drugs" and "potential toxin" renders claims 63 indefinite as they are not defined by the claim, the specification does not teach what the "potential drugs" and "potential toxin" encompass.

Section 2171 of the M.P.E.P. states

> *There are two separate requirements set forth in this paragraph:*
> *(A) the claims must set forth the subject matter that applicants regard as their invention; and*
> *(B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.*
>
> *The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.*

In the instant case, one of skill in the art could find representative examples in the art which have been defined in such terms, however, it is unclear at what point one of skill in the art would be infringing on the claims without limitations as to the metes and bounds of what is encompassed by the term terms "potential drugs" and "potential toxin".

Additionally, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 63 recites the broad recitation "components from physiological or pathological processes", and the claim also recites "including microbes" which is the narrower statement of the range/limitation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 28, 30-34, 37, 38, 40-61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitation of "i) seeding solitary cells in a soft agar medium with or without growth factor, ii) incubating said cells in a low gelling temperature gel at a suitable temperature and atmosphere with said agent having an activity on clonal growth;" claimed in Claims 28, 30-34, 37, 38, 40-61 and 63 has no clear support in the specification and the claims as originally filed. Applicants pointed pages 27 and 40 for support. A review of the cited support reveals support for growing the cells sparsely in soft agar medium and the agar being low gelling temperature agarose. The suggested support is not found persuasive because there is nothing in the specification to suggest taking the cells first seeded in a soft agar medium and subsequently incubating said cells from the soft agar medium in a second low gelling temperature gel. The subject matter claimed in amended claims 28, 30-34, 37, 38, 40-61 and 63 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 28, 30, 31, 34, 38, 40, 41, 42, 43, 44, 46, 47, 50-53, and 59-63 are rejected under 35 U.S.C. 102(b) as being anticipated by USPN 5,597,798 (Howell et al. 1997) evidenced by YourDictionary.com (http://www.yourdictionary.com/food, 10/4/2010) in view of Bagasra et al. (Cancer Immunol. Immunotherap. 1985 20:55-600).

Howell et al. teach testing the sensitivity of tumor cells to treatment with epidermal growth factor (EGF) and the drug/toxin cisplatin (DDP) by treating tumor cell lines established from patients in colony forming assays *in vitro* in which the cells were grown in serum, which contains serum factors for clonal cell growth. Howell et al. teach using soft-agar assays with low melting temperature agarose. Low melting temperature agarose has a low gelling temperature. See Bagasra et al. p.56-2nd col. Howell et al. teach trypsinizing, re-suspending, and plating the cells in soft agar, which would result in plating of at least some solitary cells. See abstract, col. 4-6, and Fig. 1. Howell et al. teaches incubating the cells with the EGF and cisplatin before plating them in soft agar. Howell et al. teaches that EGF enhances cytotoxicity of cisplatin and other chemotherapeutic agents. See col. 10-12.

Howell et al. teach testing the sensitivity of tumor cells to EGF and cisplatin in tumor xenograft assays and their effect on tumor growth. Howell et al. teach that EGF enhanced the anti-tumor activity of EGF in this anti-tumor assay by enhancing cell-kill. See col. 11 and 12 and Fig. 4.

Howell et al. teach testing determining the toxicity of EGF and cisplatin *in vivo* on the level of white blood cells and neutrophils. The administration of EGF and cisplatin would immunize and stimulate immune cells to these products. Howell et al. teach that while EGF enhances cisplatin toxicity in cancer cells, it does not alter the toxicity of cisplatin to these immune cells. See col. 12 and 13.

Howell et al. teach that EGF can be used to modulate sensitivity to various therapeutics and teach treating subjects with EGF and cisplatin and other chemotherapeutics. The subjects, including humans, would be at risk of developing the disorders of claims 52 and 53. See col. 13 and 18-20.

The analogues of claim 51 would encompass EGF and cisplatin and the other chemotherapeutics of Howell et al. as they would have analogous activity and the analogues are not limited.

Additionally, given that EGF is a protein from animals and can be used to produce energy and stimulate growth and in absence of a limiting definition of food or food additives, EGF would be encompassed by food and food additives. See YourDictionary.com (http://www.yourdictionary.com/food, 10/4/2010). It is also a component of physiological processes. Additionally, the term food additive is merely suggestive of intended use, i.e. adding something to food, which does not distinguish the agents from the prior art and the agents of Howell et al. could be readily added to food for treatment and thus would be food additives.

With regard to claim 38, a wherein clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited, MPEP 2111.04.

Howell et al. does not specifically teach treating the cells with the agents in the low gelling temperature gel or that the cells were solitary cells.

Bagasra et al. teach that low gelling and melting point agarose for soft/semi-solid agar studies of anchorage independent tumor growth has several advantages over agar containing media including ease of preparation and use and the ability to store stock solution for extended periods. See abstract, Introduction, and p.59-1st col. Bagasra et al. teach vigorous mixing of the cells in the agarose/agar to equal distribute the cells and eliminate cell aggregates. See Plating of cells-p.56. It is noted that the claimed soft agar encompasses agarose. See p. 27-line 10-11 of the instant specification.

It would have been *prima facie* obvious at the time the invention was made to modify the method of Howell et al. and directly treat the cells in the low gelling temperature agarose with the agents as this is a simple rearrangement of known elements and one would be motivated to see if the timing of the addition of the agents altered their effectiveness. Furthermore, it would have been *prima facie* obvious at the time the invention was made to use solitary cell suspensions as taught by Bagasra et al. to ensure colonies are growing from single cells and the colonies counted are not cell aggregates present from the improper separation and seeding of cells at the beginning of the assay.

15. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 5,597,798 (Howell et al. 1997) in view of Bagasra et al. (Cancer Immunol. Immunotherap. 1985 20:55-600), in view of De Asua et al. (Proc. Natl. Acad. Sci. USA, 1973, 70:1388-1392 of record) and in view of Kamei H. (Cell Biol. Int. Rep. Jan. 1987, 11 (1): 35-41, of record).

Claim 33 is drawn to the method according to claim 29, wherein the cells are selected from the group consisting of BHK21/c13, and BHK21/C13 cells transformed with polyoma virus.

Howell et al. and Bagasra et al. teach as set for above, but do not teach using BHK21/c13, and BHK21/C13 cells transformed with polyoma virus.

De Asua et al. teach testing the effect of insulin and cAMP on BHK21/13 agar colony formation, see Abstract and Table 1.

Kamei H. teaches that the BHK21/13 cells of De Asua cells are BHK21/c13 cells, see Introduction p. 35. Kamei et al. also teaches using a BHK21/c13 clone to study the effects of retinoic acid on anchorage independent growth of the BHK21/c13 clone cells, see Abstract.

It would have been *prima facie* obvious at the time the invention was made to use the BHK21/c13 cells of De Asua in combination with the method of Howell et al. to determine the effect of EGF and cisplatin or chemotherapeutics of Howell et al. on BHK21/c13 cell anchorage independent growth and tumor formation. One of skill in the art would have been motivated to use BHK21/c13 cell cells to determine the breadth of EGF and cisplatin activity on different cell types. As the skill in the art is high, one of skill in the art would have had a reasonable expectation of success of using BHK21/c13 cells as they were a well known model for assaying the effects of agents in *in vitro* cell studies of clonal cell growth. Additionally, the simple substitution of known cell lines would be obvious to one of skill in the art because the cells would predictably be effective for selecting an agent that has an activity on clonal growth given that the BHK21/c13 cells were used in the art for screening activity of anti-tumor agents.

16. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 5,597,798 (Howell et al. 1997), in view of Bagasra et al. (Cancer Immunol. Immunotherap. 1985 20:55-600), and in view of US Pat. No. 4,744,985 (Tami et al. May 17, 1988, of record).

Claim 37 is drawn to the method according to claim 36, wherein said tumor cells are transplanted Ehrlich carcinoma cells.

Howell et al. and Bagasra et al. teach as set for above, but do not teach tumor cells are transplanted Ehrlich carcinoma cells.

US Pat. No. 4,744,985 teaches using Ehrlich tumor cells transplanted intraperitoneally or into the armpits of mice to determine the anti-tumor activity of bacterial extracts, see cols.20-24.

It would have been *prima facie* obvious at the time the invention was made to use the Ehrlich tumor cells of US Pat. No. 4,744, 985 in the examination of tumor growth/metastasis in the method of Howell et al. to determine the effect of EGF and cisplatin on transplanted Ehrlich tumor cell growth and metastasis. One of skill in the art would have been motivated to use Ehrlich tumor cells to determine the breadth of EGF and cisplatin activity on different tumor types. As the skill in the art is high, one of skill in the art would have had a reasonable expectation of success of using Ehrlich tumor cells as they were a well known model of tumor formation. Additionally, the simple substitution of known cell lines would be obvious to one of skill in the art because the cells would predictably be effective for selecting an agent that has an activity on clonal growth given that the Ehrlich tumor cells were used in the art for screening activity of anti-tumor agents.

17. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 5,597,798 (Howell et al. 1997), in view of Bagasra et al. (Cancer Immunol. Immunotherap. 1985 20:55-600) and further in view of Lim et al. (Jpn. J. Cancer Res. 93: 36-41, Jan. 2002).

Claim 45 is drawn to the method according to claim 28, wherein the agent is a microbe.

Howell et al and Bagasra et al. teach as set forth above, but do not teach using a microbe.

Lim et al. teach that lactic acid bacteria are known to have beneficial effects on the host such as preventing carcinogenesis. Lim et al. teach that the lactic acid bacteria strain, *Lactobacillus rhamnosus* GG (LGG), when fed to mice implanted with bladder cancer cells, reduced the tumor burden. See abstract, Fig. 1, Fig. 3, p. 38-left col. Lim et al. teach that LGG increased the level of spleen CD3, CD4, CD8a T lymphocytes, and natural killer cells and there was an increase of lymphocytes and granulocytes in tumor sections. See abstract, Fig. 2 and 4, Tables I and II. Lim et al. teach that LGG taken orally could be a potential and convenient adjunct therapy for bladder cancer. See p. 40-2nd col.

It would have been *prime facie* obvious to combine the teachings of Howell et al. and Lim et al. at the time the invention was made and test the LGG microbe in combination with EGF and/or cisplatin, or the other chemotherapeutics of Howell using the method of Howell to potential identify combination of agents with enhanced anti-tumor activity. One would have been motivated with a reasonable expectation of success as the agents of Howell et al. and Lim et al. were shown to be effective anti-tumor agents, Howell et al. teaches EGF enhances anti-tumor activity, the tests were well known in the art, and more effective anti-tumor agents would be beneficial for cancer treatment.

18. Claims 28, 30-32, 34-36, 38-41, 43, 44, 46, 47, 50-53, 59, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prechel et al. (Cancer Letters, 1995, 92: 235:242, of record) as evidenced by Car et al. (Toxicologic Pathology, 1999, Vol. 24:58-63, of record) in view of Bagasra et al. (Cancer Immunol. Immunotherap. 1985 20:55-600).

Prechel et al. teach testing the effect *in vivo* effect of IL-12 on colony formation of myeloid cells in mice that had been immunized with Lewis lung carcinoma LLC-LN7 tumor cells with IL-12, which stimulates the growth of myeloid colonies, see p. 237-2nd col. figure 1, and Table 1. Prechel et al. teach testing the effect of IL-12 on colony formation of myeloid cells *in vitro* by seeding bone marrow and spleen cells in 1 ml of semisolid agar (soft) in RPMI-1640 medium supplemented with 20% FBS and 0.3% agar, which would seed at least some solitary cells. See p.236, p. 237-2nd col. and Fig. 2. This colony forming assay would clone and select cells for cells that grow in the presence of IL-12 that are from mice immunized with LLC-LN7 tumor cells. Prechel et al. teach injecting mice with tumor cell, treating with IL-12 and determining the effect of palpable local tumor size and the formation of metastatic lung nodules and the T-cell proliferative capacity of spleen cells bearing the injected tumor cells. See p.236 and 240 and Fig. 2, 3 and 6. With regard to claim 38, a wherein clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited, MPEP 2111.04.

Car et al. teach that IL-12 is a heterodimeric cytokine produced by several types of cells that is used as a drug, but also has toxic effects, see p. 58. Thus, IL-12 is drug, toxin, and a component of a physiological process.

Additionally, the term food additive is merely suggestive of intended use, i.e. adding something to food, which does not distinguish the agents from the prior art and the agents of Prechel et al. could be readily added to food for treatment and thus would be food additives.

Additionally, IL-12 is encompassed by the broadly claimed analogues of claim 51. Furthermore, with regard to claims 47, 50, and 59, IL-12 functions to stimulate colony formation, while reducing cell proliferation in bone marrow and spleen in vivo. See Fig. 1 and 2. Thus, at effective does IL-12 has the ability to either stimulate or inhibit different aspects of clonal cell growth, i.e. colony formation and proliferation. Furthermore, the clonal mitotic inhibitor or stimulator of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor or stimulator used in claims 47, 50 and 59 need not be selected by the method of claim 28. Thus, the serum, which contains serum factors, in the culture media used to grow the LLC-LN7 tumor cells, is a clonal mitotic stimulator that stimulates clonal growth of the cultured cells. See p. 236-1st col.

Prechel et al do not specifically teach using a low gelling temperature gel or seeding solitary cells.

Bagasra et al. teach that low gelling and melting point agarose for soft/semi-solid agar studies of anchorage independent tumor growth has several advantages over agar containing media including ease of preparation and use and the ability to store stock solution for extended periods. See abstract, Introduction, and p.59-1st col. Bagasra et al. teach vigorous mixing of the

cells in the agarose/agar to equal distribute the cells and eliminate cell aggregates. See Plating of cells-p.56. It is noted that the claimed soft agar encompasses agarose. See p. 27-line 10-11 of the instant specification.

It would have been *prima facie* obvious at the time the invention was made to use the soft agarose low melting point gel of Bagasra et al. in the methods of Prechel et al. because Bagasra et al. teach the multiple advantages of using the low gelling/melting temperature agarose in soft agar assays. One would have been motivated to use the low gelling/melting temperature agarose soft agar assay to improve the ease and efficiency of the assay. Furthermore, it would have been *prima facie* obvious at the time the invention was made to use solitary cell suspensions as taught by Bagasra et al. to ensure colonies are growing from single cells and the colonies counted are not cell aggregates present from the improper separation and seeding of cells at the beginning of the assay.

19. All other objections and rejections recited in April 22, 2010 are withdrawn.

20. No claims allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642